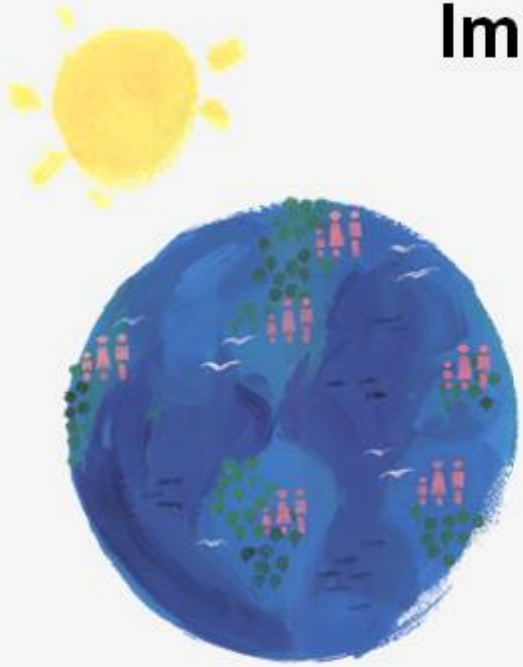
NICEATM

National Toxicology Program
Interagency Center for the Evaluation of Alternative Toxicological Methods

ICCVAM

Interagency Coordinating Committee on the Validation of Alternative Methods



Implementation of the NICEATM-ICCVAM Five-Year Plan

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Chair, ICCVAM Five-Year Plan Implementation Subcommittee
Senior Science Policy Officer
Office of the Commissioner
Food and Drug Administration

June 25, 2009
SACATM Meeting
Arlington, VA

Nt

National Toxicology Program

NIEHS

National Institutes of Health

Directive from U.S. House and Senate Appropriations Committees

Requested NICEATM-ICCVAM, in partnership with relevant Federal agency program offices, to build on the NTP Roadmap to create a five-year plan to:

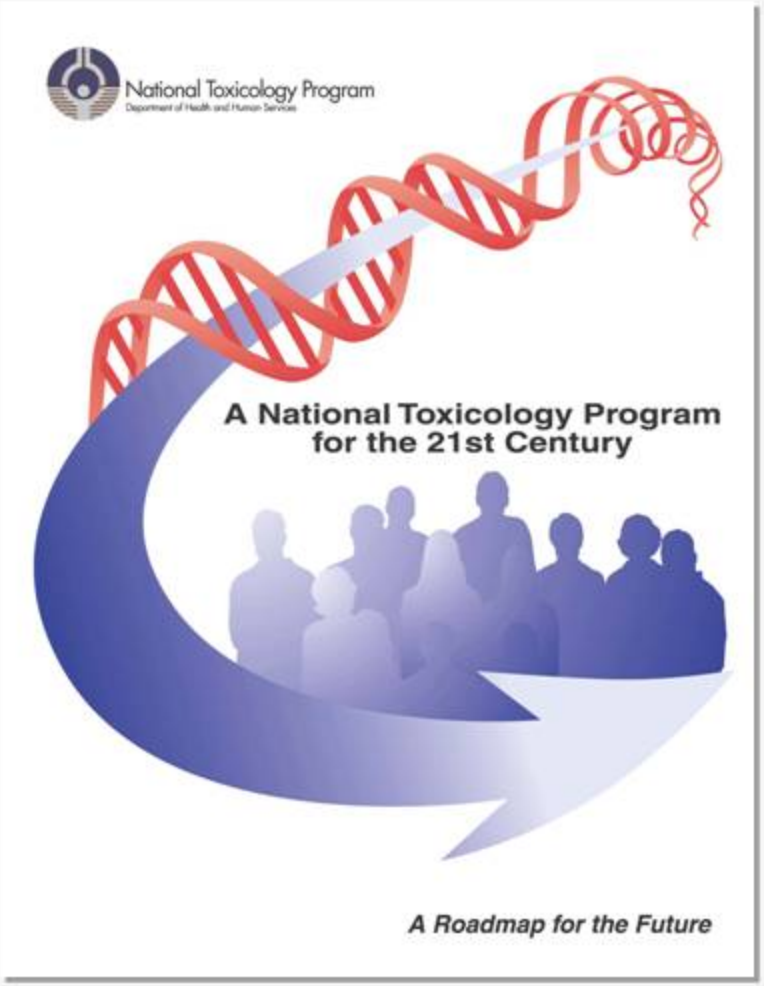
- Research, develop, translate, and validate new and revised non-animal and other alternative assays for integration of relevant and reliable methods into the Federal agency testing programs.
- Identify areas of high priority for new and revised non-animal and alternative assays or batteries of those assays to create a path forward for the 3Rs, when this is scientifically valid and appropriate.

NICEATM-ICCVAM Five-Year Plan

A plan to advance alternative test methods of high scientific quality to protect and advance the the health of people, animals, and the environment

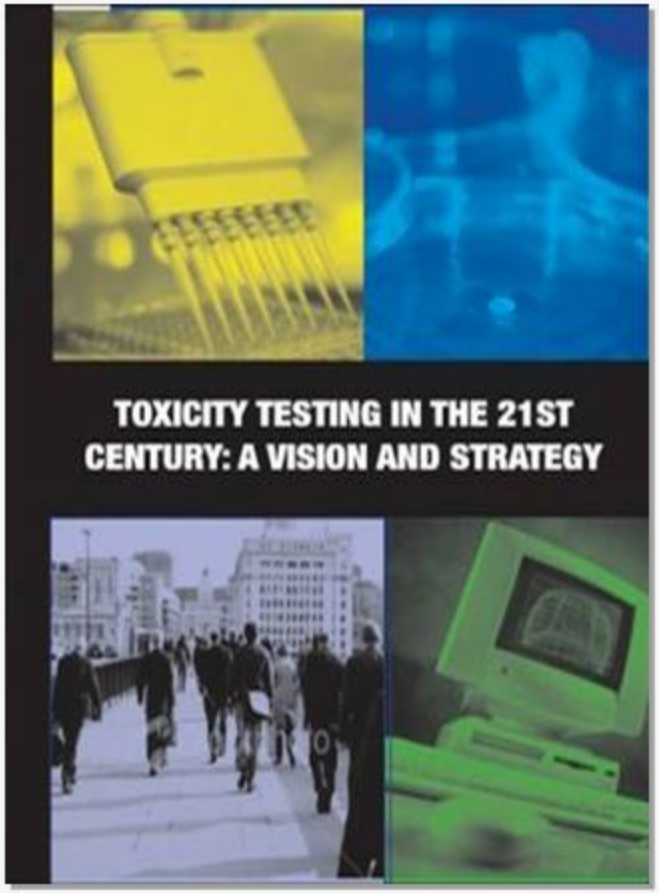
Available at http://iccvam.niehs.nih.gov/docs/5yearplan.htm

The NICEATM-ICCVAM Five-Year Plan Builds on the NTP Roadmap



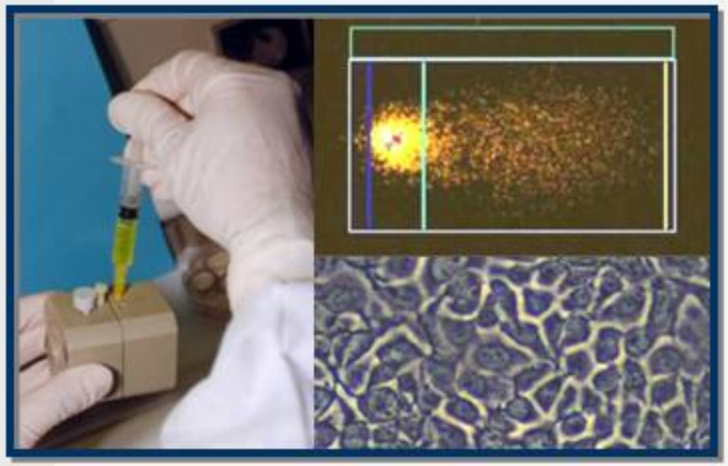
- **Goal 2 of the Roadmap**
  - *"Develop and validate improved testing methods and, where feasible, ensure that they reduce, refine, or replace the use of animals"*
- **From Page 7**
  - *"Activities and assays developed under the NTP Roadmap will be done in cooperation and consultation with ICCVAM to maximize their value to regulatory agencies."*

The NTP Roadmap and The Five-Year Plan are consistent with the recent NAS Report



- **From NAS Report:**
  - *"The use of a comprehensive array of in vitro tests to identify relevant biologic perturbations with cellular and molecular systems based on human biology could eventually eliminate the need for whole-animal testing and provide a stronger mechanistically based approach for environmental decision-making."*

The NICEATM-ICCVAM Five-Year Plan Builds on Current U.S. Laws



- **Agencies have mandates to protect human and animal health and the environment**
  - In order to fulfill these mandates, agencies must ensure that substances are safe, or properly labeled if hazardous
- **Agencies must determine if alternative test methods can provide equal or better protection before their adoption or endorsement**
  - The ICCVAM Authorization Act of 2000 requires that new, revised, and alternative test methods must be determined to be at least equivalent for risk assessment purposes

[1] ICCVAM Authorization Act of 2000, 42 U.S.C. 285*l*–3

The Five-Year Plan Builds on Current U.S. Animal Protection Laws, Policies, and Regulations

- U.S. laws, policies, and regulations require, prior to the use of animals for research and testing, that available alternatives must be considered and used where appropriate that will[1]:
  - **Reduce** the number of animals to the minimum required to obtain scientifically valid data
  - **Refine** procedures to lessen or eliminate pain and distress to animals
  - **Replace** animals with non-animal systems or with a phylogenetically lower animal species

[1]All of ICCVAM's activities are grounded in the *U.S. Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training*
http://grants.nih.gov/grants/olaw/references/phspol.htm#USGovPrinciples

Five-Year Plan: Roles of ICCVAM and NICEATM

- NICEATM and ICCVAM ***promote and facilitate*** research, development, translation, and validation activities
  - ICCVAM depends on other stakeholder organizations to conduct and achieve successful test method research, development, translation, and validation
  - ICCVAM reviews test method submissions from stakeholders to determine the validation status (usefulness and limitations) of new and revised test methods
- Federal agencies with research, development, translation, and/or validation activities:
  - Department of Defense
  - Department of Energy
  - Environmental Protection Agency
  - Department of the Interior
  - NIEHS/NTP
  - Food and Drug Administration
  - NIOSH
  - ATSDR
  - NIH Office of the Director
  - National Cancer Institute
  - Department of Agriculture

Implementation of the Five-Year Plan

- An overall goal is for ICCVAM to assume a greater leadership role in promoting research, development, translation, validation, and regulatory acceptance of alternative test methods.
- NICEATM and ICCVAM developed a Five-Year Plan that builds on the ICCVAM mission, vision, and strategic priorities to achieve progress and to inform the public of their plans and approaches.
- To implement this plan, NICEATM and ICCVAM will work with a broad range of stakeholders, including Federal agencies, national and international validation and test guideline organizations, industry, academia, and the animal welfare community.
  - Success will depend on these interactions both within and outside of ICCVAM agencies.
  - ICCVAM will take a proactive leadership role and identify and develop collaborations that will include experienced scientists that can bring state-of-the-art science to the forefront.

Implementation of the Five-Year Plan: Cooperation is Essential

- ICCVAM, as an interagency committee, **does not have resources to conduct research, development, and validation studies**.
- Therefore, successful implementation will depend on interactions both within and outside of ICCVAM agencies.
- ICCVAM **depends on its many stakeholders** to conduct and achieve successful test method research, development, translation, and validation efforts.
- Several Federal agencies are responsible for safeguarding human and animal health and the environment.
  - New and revised toxicological test methods are being developed with increasing frequency as scientists seek to incorporate new science and technology.
- ICCVAM and NICEATM serve a unique role in helping to evaluate the usefulness and limitations of these methods and achieving the acceptance of those found to be scientifically valid for regulatory purposes.
- **Interagency cooperation via ICCVAM provides an efficient and effective mechanism for Federal test method review and helps to ensure that new and revised test methods meet the needs of Federal agencies while reducing, refining and replacing the use of animals in safety testing where scientifically feasible.**

Overview of the Implementation Plan: Four Key Challenges

- The Implementation Plan is a working document that describes how NICEATM and ICCVAM are implementing the strategies outlined in the Five-Year Plan.
- Implementation activities address the four key challenges in the Five-Year Plan:
  1. **Identify Priorities and Conduct and Facilitate Activities in These Areas**
  2. **Identify and Promote New Science and Technology**
  3. **Foster Regulatory Acceptance and Use of Alternative Test Methods**
  4. **Develop Partnerships**

Challenge 1: Identify Priorities and Conduct/Facilitate Activities in These Areas

- ICCVAM test method prioritization criteria
  1. Potential impact on reducing, refining, or replacing animals for testing
  2. Potential to improve prediction of adverse health or environmental effects
  3. Applicability to multiple agencies
- Priorities may vary across agencies
- Priorities may change
  - Need to be flexible so we can take advantage of advances in science and technology and availability of new methods

Challenge 1: Identify Priorities[1] and Conduct/Facilitate Activities in These Areas

- Four highest priority areas
  - Biologics/Vaccines
  - Ocular Toxicity
  - Acute Toxicity
  - Dermal Toxicity
- Other priority areas
  - Immunotoxicity
  - Endocrine Disruption
  - Pyrogen Testing
  - Reproductive/Developmental Toxicity
  - Chronic Toxicity/Carcinogenicity Testing

[1]These priorities are likely to evolve in response to new testing needs and advances

Biologics/Vaccines Testing: Priority and Planned Activities

- **Basis for High Priority:**
  - *Vaccine potency testing accounts for more animals experiencing pain and distress without analgesics, anesthetics, or tranquilizers on the USDA annual report than any other testing procedure*
  - Multiple regulatory agencies require such testing
- **Planned activities include**:
  - Developing a scientific workshop to evaluate:
    - The state of the science for possible alternatives
    - Use of humane endpoints in *in vivo* potency tests.
  - Evaluate *in vitro* Potency Tests for Leptospirosis vaccines being developed by the U.S. Department of Agriculture (USDA) and Michigan State University
- **Progress**:
  - ICCVAM Biologics Working Group (BWG) reconstituted to address these activities
  - Workshop will be scheduled for 2010

Ocular Safety Testing: Priority and Planned Activities

- **Basis for High Priority:**
  - Potential for significant pain and distress; one of four most common safety tests
  - Multiple regulatory agencies require testing to identify ocular hazards to warn consumers and workers
- **Planned activities include**:
  - Review routine use of topical anesthetics and systemic analgesics to avoid or minimize pain and distress
  - Foster non-animal methods to detect permanent eye damage
  - Assess non-animal methods to detect reversible eye damage
  - Collect reference data to facilitate validation studies
  - Evaluate new methods or combinations/batteries of *in vitro* methods
- **Accomplishments**:
  - Convened a May 19-22, 2009 international independent scientific peer review panel to evaluate alternative test methods and approaches that may further reduce and refine the use of animals for ocular safety testing (discussed as a separate agenda item later today).
  - 2008:Submitted draft OECD Test Guidelines for bovine corneal opacity and permeability (BCOP) and isolated chicken eye (ICE) test methods; **accepted by OECD NCs in April 2009** (discussed as a separate agenda item today).

Acute Systemic Toxicity Testing: Priority and Planned Activities

- **Basis for High Priority:**
  - Toxic substances can cause significant pain and distress; Most common safety test conducted
  - Multiple regulatory agencies require testing to identify poisonous substances to warn consumers and workers and to determine appropriate packaging and transport precautions
- **Planned activities include**:
  - Organize an international workshop to identify earlier, more humane endpoints and predictive batteries of *in vitro* test methods
  - Work with stakeholders to promote the collection and submission of *in vitro* and *in vivo* toxicity test data to ICCVAM in order to advance the development and validation of more predictive *in vitro* test methods (or batteries of tests) and earlier, more humane endpoints for acute systemic toxicity testing
  - Participate on an international Validation Management Group for a human hepatic biotransformation enzyme induction assay using HepaRG cells and cryopreserved human hepatocytes
- **Accomplishments**:
  - A workshop on *Acute Chemical Systemic Toxicity Testing – Strategies for Developing and Advancing More Humane Endpoints and In Vitro Alternatives* convened on February 6 – 7, 2008 (http://iccvam.niehs.nih.gov/methods/acutetox/Tox_workshop.htm)
  - Drafted an OECD Guidance Document on *Using Cytotoxicity Tests To Estimate Starting Doses For Acute Oral Systemic Toxicity Tests*

Dermal Toxicity Testing: Priority and Planned Activities

- **Basis for High Priority:**
  - Potential for significant pain and distress; one of top four most common safety tests
  - Multiple regulatory agencies require testing to identify irritating and corrosive substances to warn consumers and workers and to determine appropriate transport requirements
- **Planned activities include**:
  - Evaluate alternative dermal irritation test methods for their usefulness and limitations in U.S. regulatory testing
  - Assist in the development of an Organisation of Economic Co-operation and Development (OECD) Test Guideline for human skin model systems for skin irritation testing.
  - Evaluate a combination (or battery) of *in vitro* test methods for evaluating skin corrosivity and irritation
  - Conduct a study to evaluate potential false negative corrosive chemicals in proposed *in vitro* dermal irritation assays
- **Progress**:
  - Submitted proposed updated OECD Test Guidelines for *in vitro* skin corrosivity test methods to include ICCVAM-recommended performance standards in order to facilitate expedited validation of improved versions of current tests
  - Participated in 2008 and 2009 OECD Expert Consultations on *In Vitro* Dermal Irritation Methods

Allergic Contact Dermatitis Testing: Priority and Planned Activities - 1

- **Basis for High Priority:**
  - Potential for significant pain and distress; one of four most common safety tests
  - Multiple regulatory agencies require that substances that could induce an allergic skin reaction be identified to warn consumers and workers
- **Planned activities include**:
  - Evaluate the validation status of:
    - The reduced LLNA test method
    - Modified LLNA protocols that do not use radioactivity
    - The LLNA as a stand-alone assay for potency determination for classification purposes
    - The LLNA for testing formulations, aqueous solutions, and metals
  - Develop LLNA test method performance standards to efficiently evaluate the validity of modified versions of the LLNA
  - Review and comment on computational and *in vitro* methods proposed for incorporation into testing strategies for identifying potential skin or lung sensitizers

Allergic Contact Dermatitis Testing: Priority and Planned Activities - 2

- **Progress and Accomplishments**:
  - Convened two independent expert peer review panel meetings (March 2008 and April 2009) to evaluate the validation status of new versions and applications of the LLNA (discussed as separate agenda items).
  - Developed harmonized LLNA performance standards in conjunction with ECVAM and JaCVAM
  - 2009: submitting draft updated OECD TG 429 (the LLNA) to include the rLLNA and performance standards
  - 2009: submitting two new draft TGs for non-radioactive versions of the LLNA (in conjunction with JaCVAM)

Endocrine Disruptor Testing: Priority and Planned Activities

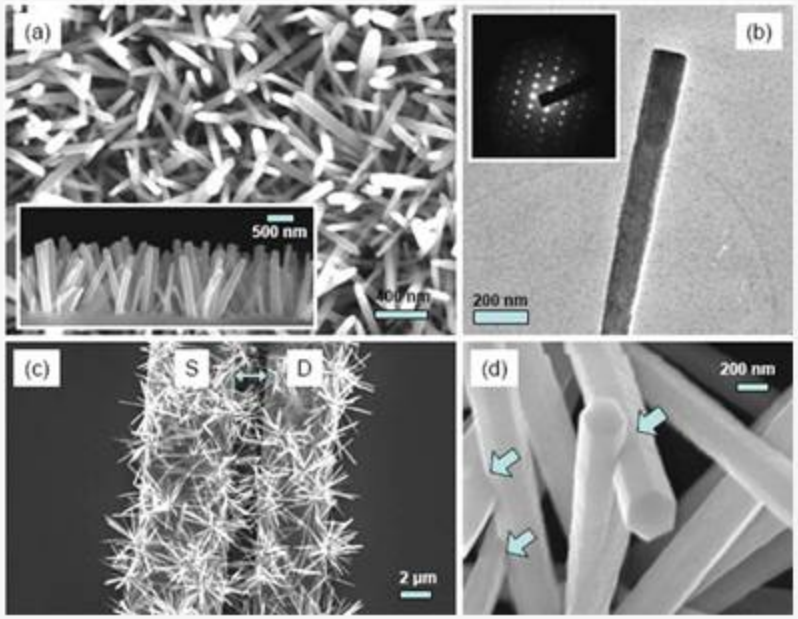
- **Basis for High Priority:**
  - Multiple regulatory agencies require that substances that could affect hormone levels be identified to warn consumers and workers
  - Potential for large numbers of animals; potential pain and distress
- **Planned activities include:**
  - Complete a joint international study with ECVAM and JaCVAM of the LUMI-CELL assay, and estrogen receptor transcriptional activation assay (ER TA)
  - Use the validation study results to develop a high quality *in vitro* ER TA database and test method performance standards
  - Provide support in designing studies for the validation of the MCF-7 Cell Proliferation Assay protocols to detect both estrogenic and anti-estrogenic activity
  - Contribute to development of an OECD Test Guideline for using stably transfected transcriptional activation assays to screen for substances that may affect estrogen activity
- **Progress**
  - Validation studies continuing

Challenge 2: Identify and Promote New Science and Technology

- Areas currently identified as potentially applicable
  - High Throughput Screening
  - Other Animal Systems (Lower Species)
  - Computational Approaches
  - Biomarkers of Toxicity
  - Development of Toxicology Databases
  - Testing Strategies for Nanomaterials
- Most of these areas will require several years of research and development
- ICCVAM and NICEATM will continuously monitor federal agency and other stakeholders' research activities to identify those with potential applicability
- **Progress: Established ICCVAM Research and Development Working Group (RDWG)**
  - The RDWG will assist NICEATM and ICCVAM in identifying and promoting research incorporating new technologies expected to support future development of new test methods and approaches that will reduce, refine, and replace animal use in toxicity testing

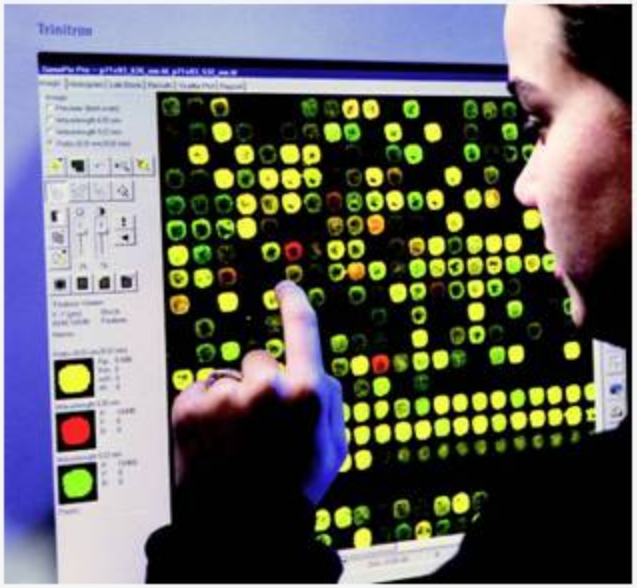
Testing Strategies for Nanomaterials : Priority and Planned Activities

- **Planned activities include**:
  - Assess the state of the science to determine if developing a scientific workshop to evaluate possible alternatives is warranted.
  - Develop a one-day symposium to define the current planned activities with ICCVAM agencies that are relevant to nanomaterials testing and the use of alternative methods
  - Engage in OECD activities relevant to alternative test methods intended for safety testing of nanomaterials



High Throughput Screening: Priority and Planned Activities

- **Planned activities include**:
  - Monitor progress in collaborations between research institutes within NIEHS, EPA, and NIH that will test a large number of compounds broadly characterizing and defining the chemical-biological space occupied by chemicals of toxicological concern
  - Nominate substances identified by NICEATM-ICCVAM as reference compounds for the development of alternative test methods as well as other compounds that have been tested in various alternative test methods, in the standard *in vivo* toxicity tests, or in humans

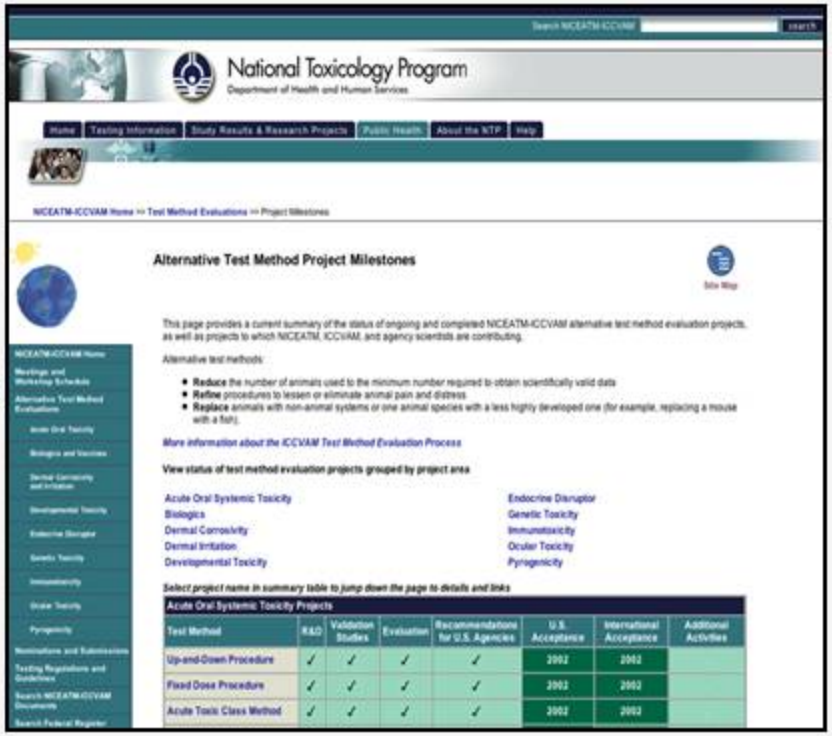


Challenge 3: Foster Regulatory Acceptance and Use of Alternative Test Methods - 1

- Once regulatory authorities have accepted an alternative test method, ICCVAM will work to promote its use by broadly communicating such outcomes
- How will ICCVAM foster acceptance and use?
  - Provide guidance on adequate validation study design to ensure data is generated to support test method acceptance decisions
  - Carry out high-quality public independent peer reviews
  - Provide comprehensive test method evaluations to regulatory agencies
    - Provides validation status for regulatory applications
    - Provides assessment of performance compared to existing methods
  - Organize implementation workshops for stakeholders

Fostering Regulatory Acceptance and Use of Alternative Test Methods - 2

- **Planned Activities**
  - Create ICCVAM agency webpages dedicated to their specific activities associated with alternative test methods research, development, translation, and validation.
  - Create a web-based database of all test methods that have been reviewed or that are currently undergoing review
- **Accomplishments**
  - NICEATM-ICCVAM website updated to include a summary table listing the status of all test methods reviewed or currently under review, including their development, validation, evaluation, and national and international regulatory acceptance status



ICCVAM
NICEATM

Challenge 4: Develop Partnerships and Strengthen Interactions with ICCVAM Stakeholders - 1

- Effective interactions necessary to stimulate alternative test method research, development, translation, and validation *by stakeholders*
- Partnerships will:
  - Leverage and optimally utilize available resources
  - Maximize efficiency/minimize duplication of efforts
  - Ensure early exchange of information
  - Facilitate national and international recognition, acceptance, and implementation of scientifically valid test methods
- Collaborate with ECVAM and JaCVAM to carry out independent validation studies and test method evaluations

Developing Partnerships and Strengthening Interactions with ICCVAM Stakeholders -2

Planned Activities

- Collaborate with government and non-governmental organizations, where appropriate, to co-sponsor workshops to evaluate the state-of-the-science related to the development and validation of alternative toxicological test methods
  - Also to identify high priority research, development, translation, and validation activities necessary to advance and characterize the usefulness of such methods.
- Facilitate the international adoption of valid alternative test methods by providing standardized protocols that can be considered for adoption by international organizations
- Work with other national and international validation organizations (for example, ECVAM and JaCVAM) to promote ICCVAM's validation and acceptance criteria, which have been substantially incorporated into OECD Guidance Document 34, and to consider other issues related to validation as they occur.

Developing Partnerships and Strengthening Interactions with ICCVAM Stakeholders - 3

Recent Progress and Accomplishments

- **Memorandum of Cooperation signed for International Cooperation on Alternative Test Methods (ICATM), April, 2009**
- ICCVAM, in conjunction with stakeholders in the United States, the European Union (EU), and Japan, drafted OECD Test Guidelines (TGs) for the ICE and BCOP test methods.
  - Once formally adopted by the OECD Council, data generated with these TGs will be accepted by all 30 OECD member countries in accordance with OECD Mutual Acceptance of Data.
  - The use of these TGs will reduce the use of rabbits for eye safety testing and eliminate such testing in animals of most substances likely to cause severe pain and discomfort.
- NICEATM, in conjunction with the ICCVAM Acute Toxicity Working Group, drafted an OECD Guidance Document entitled "*In Vitro* Neutral Red Uptake (NRU) Cytotoxicity Tests for Estimating Starting Doses for Acute Oral Systemic Toxicity Tests".
  - The standardized protocols on which this draft GD is based were developed during a NICEATM/ICCVAM/ECVAM sponsored international validation study.
- NICEATM and the ICCVAM Genetic Toxicity Working Group (GTWG) are involved in development of a draft OECD TG for the *in vitro* mammalian cell micronucleus assay and have provided comments on a study to determine the most appropriate measure of cytotoxicity for inclusion in the TG

Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)

Consumer Product Safety Commission
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- *Kristina Hatlelid, Ph.D.*
- *Joanna Matheson, Ph.D.*

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ICCVAM Five-Year Plan Implementation Subcommittee

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- Dr. David Hattan, CFSAN, FDA
- Dr. Abigail Jacobs, CDER, FDA
- Dr. Vasant Malshet, CDRH, FDA
- Dr. Jodie Kulpa-Eddy, USDA
- Dr. Margaret Snyder, NIH
- Dr. William Stokes, NIEHS
- Dr. Raymond Tice, NIEHS
- Dr. Marilyn Wind, CPSC
- Dr. Jack Fowle, OPP, EPA
- Dr. Amy Rispin, OPP, EPA (to Jan, 2009)

Thank you for your attention. Questions?

Dr. Suzanne Fitzpatrick

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Questions for SACATM

Please comment on the extent that the draft Implementation Plan addresses the following four key challenges and related activities proposed in the 5-Year Plan:

1. **Identify Priorities and Conduct and Facilitate Activities in These Areas**
2. **Identify and Promote New Science and Technology**
3. **Foster Regulatory Acceptance and Use of Alternative Test Methods**
4. **Develop Partnerships**